Appendix 2

Starchy foods and prevention of type 2 diabetes mellitus – a systematic review exploring the protective mechanisms

Marion G. Priebe
Roel J. Vonk

Submitted

Abstract

In prospective cohort studies foods that elicit low postprandial glycemia or whole grain foods, rich in non-digestible carbohydrates and cereal fiber-associated phytochemicals, have been shown to reduce the risk of developing type 2 diabetes (T2DM). However, it is not clear whether reduced glycemia or physiological effects associated with the presence of non-digestible carbohydrates determine these possible preventive effects. The aim of this systematic review was to examine the current experimental evidence for the T2DM-preventive potential of those characteristics. Therefore, we summarized results from intervention studies in healthy persons or persons at risk of developing T2DM that examined the effect of the specific food characteristics on factors involved in the pathogenesis of T2DM. In total 35 studies met the inclusion criteria. There is no evidence of a beneficial effect of decreased postprandial glycemia on hepatic insulin sensitivity (IS). The evidence for a beneficial effect on whole-body or peripheral IS is limited. More evidence is available for a beneficial effect of increased consumption of non-digestible carbohydrates on glucose tolerance and whole-body IS independent of any effect on postprandial glycemia. Whether these effects are mediated mainly by colonic fermentation of non-digestible carbohydrates or by cereal fiber-associated phytochemicals, needs to be further explored. Only a few trials examined the effect of increased intake of phytochemicals on oxidative stress or inflammation markers. The effect on other risk factors for T2DM was also scarcely investigated. In conclusion, there seems to be more evidence for the beneficial effect of non-digestible carbohydrates on IS than for the reduction of postprandial glycemia.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide and is expected to double in the next 30 years to reach 366 million in 2030 (1). Besides the loss of quality of life for the individuals concerned, this poses enormous economic as well as social costs to societies, which calls for preventive measures. Although genetic elements are involved in the pathogenesis of T2DM, the rapid increase in incidence rates suggests a particularly important role for environmental factors. Besides physical activity, diet is thought to play a key role as a modifiable risk factor. A diet increasing the risk of the development of T2DM has been defined as high in saturated fat and energy-dense foods as well as low in fruit and vegetables (2), while the role of starchy foods is still unclear.

Starchy foods (cereal grain, potatoes and products derived from them) are important components of the diet and are very diverse concerning their composition and metabolic impact. Suggestive evidence for the preventive role of certain types of starchy foods is currently available from prospective cohort studies. Inverse associations between diets either with low glycemic index (GI) foods or with whole grain foods and the development of T2DM have been found (3;4).

Based on the results of these studies, hypotheses are put forward concerning the beneficial characteristics of starchy foods and the protective physiological mechanisms involved. Reducing postprandial glycemia, on the one hand, is inherent to low GI foods. But reduced glycemia can be achieved in various ways, like the addition of fat, resistant starch or dietary fiber and each of these components can have its own effect in relation to reducing risk factors. A low GI is also a characteristic ascribed to whole grain products, although this is dependent on the way the product has been processed. Wholemeal bread made from fine flour and breakfast cereals have a high GI (5). On the other hand, whole grain foods by definition are rich in cereal fiber and, depending on their processing also rich in resistant starch. These non-digestible carbohydrates can be, but are not necessarily present in low GI starchy foods. The effect of the presence of cereal fiber and resistant starch on postprandial blood glucose is expected to be minimal. Therefore, other physiological mechanisms need to be involved in their protective effect. These could be related to fermentation metabolites because non-digestible carbohydrates can be metabolised by the colonic microbiota into short-chain fatty acids; recently it became clear that short-chain fatty acids not only play a role in the colonic environment but can also exert effects on peripheral tissue (6–8).

Furthermore, the presence of cereal fiber in whole grain products is associated with a high content of micronutrients and phytochemicals, which also can influence various metabolic processes related to the development of T2DM. Thus, until now, it is not clear whether the reduction of the glycemic response or the physiological effects associated with the presence of non-digestible carbohydrates determine the possible preventive effect of starchy foods on T2DM.

Several randomized controlled trials and controlled clinical trials have been conducted to assess the effect of diets with a low GI, a high amount of cereal fiber, a high amount of resistant starch and a high intake of whole grain food on factors implicated with the development of T2DM. The results of these trials can provide information about the relative importance of the described characteristics in their proposed preventive effect on T2DM. Based on this, the possible underlying physiological mechanisms can be explored and further research needs can be identified. Therefore, this review addresses the following question:

What is the experimental evidence that a diet characterized by either a low postprandial glycemia or a high content of cereal fiber or resistant starch beneficially influences factors involved in the pathogenesis of T2DM in healthy adults or adults at risk of developing T2DM?

A short overview will first be given about the factors that are currently implicated with the pathogenesis of T2DM in order to highlight possible intermediate endpoints of the disease which are addressed in this review.

Factors involved in the pathogenesis of T2DM

In general, T2DM will develop as a consequence of both insulin resistance as well as β-cell dysfunction (9). Underlying mechanisms leading to those defects are still the subject of debate and several different, but also partly overlapping concepts have been postulated. In addition, differentiation between the sites of insulin resistance will need more attention as it has recently been postulated that there are different prediabetic states, which are characterized either by reduced hepatic insulin sensitivity, reduced muscle insulin sensitivity or a combination of both (10).

1. Insulin resistance

There is consensus that chronic overnutrition and lack of physical activity are important causes of insulin resistance. As a consequence **adiposity** is increased and especially visceral adiposity is associated with reduced insulin sensitivity (11).

Several groups of adipose tissue derived factors are implicated with the modulation of insulin sensitivity. **Plasma non-esterified fatty acid** (NEFA) concentrations are increased in obese persons which leads to a reduction of glucose uptake in adipose tissue and skeletal muscles and in a stimulation of glucose output from the liver (12). In addition, increased plasma concentrations of NEFA result in accumulation of lipid and lipid intermediaries of fat metabolism (e.g. ceramide) in liver and skeletal muscle cells which also contributes to the development of insulin resistance (13;14). Excess fat storage may also lead to alterations in the **adipose tissue secretome**. Adipose tissue is known to secrete various signaling peptides – the adipokines – influencing among others insulin sensitivity, food intake and inflammation. Examples are the insulin-sensitizing hormone adiponectin, which is decreased in the obese and leptin with anti-hyperglycaemic and anorexigenic properties. Resistin, a product of macrophages in adipose tissue, is implicated with reduced insulin sensitivity. Furthermore, obesity has been associated with a pro-inflammatory state in which plasma concentrations of tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP) and other inflammatory mediators are increased. Low-grade inflammatory changes have been shown to precede T2DM by many years (15). Over the past few years this **inflammation** has been causally linked to the development of insulin resistance and T2DM – with the adipose tissue being apparently the predominant source of the inflammatory response (16). Endoplasmic reticulum stress, induced by metabolic derangement (16) and macrophage infiltration (15), for example, are processes postulated to cause the inflammatory response.

Another concept concerns the induction of insulin resistance by increased levels of **reactive oxygen species** (ROS) (17). Excessive macronutrient intake is one major factor associated with increased ROS production. Various cell types have been observed to release inflammatory mediators (such as IL-6 and TNF-α) in response to elevated concentrations of glucose or NEFA, which is proposed to be a consequence of oxidative stress (15;18). As one of the key mediators of this release, the transcription factor nuclear factor-κB (NF-κB) has been identified because it activates the transcription of most proinflammatory genes. Furthermore, ROS production has been shown to be increased in adipose tissue and proposed to contribute to the dysregulation of the adipose tissue secretome (19).

2. β-cell dysfunction

In the insulin resistant state normal glucose tolerance can be maintained as long as increased insulin secretion compensates for loss of insulin sensitivity. Impaired glucose tolerance and impaired fasting glucose develop as soon as insufficient insulin is produced by the pancreas to meet the metabolic demand. Diminished insulin secretion is caused by defects in the secretory function of pancreatic β-cells or loss of β-cell mass. Many persons can sustain normoglycemia in the insulin resistant state. Thus, this failure of compensatory mechanisms is considered to be due to susceptible β-cells. Factors suggested to initiate β-cell dysfunction in susceptible persons comprise among others mitochondrial dysfunction with production of ROS, glucolipotoxicity, islet β-cell exhaustion and endoplasmic reticulum stress. β-cell dysfunction is seen to increase during the course of glucose intolerance and T2DM. Some factors suggested to contribute to the progression of dysfunction are glucotoxicity, glycation stress and islet inflammation (20).

Materials and methods

Data search and sources

Studies of interest were found by searching Medline and EMBASE from 1990 till 16 April 2008. On 12 May 2009 the search was updated (limit from 01 April 2008).

Search terms for factors involved in the pathogenesis of T2DM were:

Insulin resistance, insulin sensitivity, oxidative stress, inflammation, adiposity, obesity, adipokines, adipose tissue, fatty acids, hyperglycemia, hyperinsulinemia, glucose intolerance, impaired glucose tolerance, diabetes, beta-cell, glucotoxicity, lipotoxicity, glucolipotoxicity, insulin secretion, insulin production, insulin synthesis.

Search terms for the characteristics of starchy foods were:

amylose, amylopectin, starch, glycemic index, glycemic load, whole meal, wholemeal, wholegrain, whole grain, cereal, bran.

The strategy was not limited to human studies because animal studies addressing the same topic should also be retrieved. The results of animal studies are used in the discussion, if appropriate. No language restriction was applied. In addition, reference lists of relevant reviews and included articles were searched. Articles that had cited the studies included in the review were screened in May 2009 using the citation index.

Study selection

The title and abstract of each record of the search were assessed by one reviewer. Studies were rejected if the article definitely did not meet the review's inclusion criteria; otherwise the full text of the study was obtained.

Studies were included which fulfilled the following criteria:

- Healthy adults (>18 y) or adults with one or more risk factors for developing T2DM
- Intervention trials with a randomized controlled, controlled, cross-over or parallel design.
- Minimum number of subjects per arm: six in cross- over studies, 12 in parallel studies
- One of the following outcome measurements:
  - glucose tolerance determined by the oral glucose or meal tolerance test
  - insulin sensitivity determined by the homeostatic model assessment (HOMA), euglycemic hyperinsulinemic clamp (EHC), insulin tolerance test (ITT), frequently-sampled intravenous glucose tolerance test (FSIGTT), quantitative insulin-sensitivity check index (QUICKI)
  - body composition (fat mass, lean body mass, adipocyte size)
  - beta-cell function (HOMA-β)
  - adipokine plasma concentrations
  - markers of inflammation and oxidative stress
  - non-esterified fatty acids
- Diets:
  - refined vs whole cereal grain
  - low vs high glycemic index
  - low vs high cereal fiber
  - low vs high resistant starch

The exclusion criteria were:

- energy restricted interventions,
- studies measuring acute postprandial effects,
- difference in GI was accomplished by altering the amount of starch or mono- and disaccharides,
- the grain used was not cereal grain,
- the macronutrient composition of the intervention was planned to be different.

Duplicate publications were identified by comparing publications of the same authors with respect to study populations, location, date and follow-up time of the study.

Data abstraction and quality assessment

From original reports of the studies the following data were extracted by one reviewer:

1 General information: title, authors, source, country, year of publication, duplicate publication;
2 Trial characteristics: design, duration, randomizations, concealment of allocation, blinding, checking of blinding;
3 Participants: population, exclusion criteria, number (total, per compared groups), age, gender, health condition, diagnostic criteria used to define health condition, similarity groups at baseline, medication used, assessment of compliance, withdrawals/losses to follow-up;
4 Outcomes: outcomes specified above;
5 Results: for outcomes and times of assessment (including a measure of variation), intention-to-treat analyses.
6 Interventions: length of intervention, dietary advice or diet provided, comparison interventions. The characteristics of the applied interventions were examined in detail, because it was expected that in most diets more than one of the food characteristics of interest would have been changed. Addition of cereal fiber (CF) to a meal, for example, can reduce postprandial glycemia and low GI diets often contain a higher amount of CF than high GI diets. Information about these characteristics was obtained from the publication itself or from other publications, if necessary.

In some studies other dietary comparisons or outcome measurements were used in addition to those relevant to this review. In this case only the data that addressed the objectives of this review were extracted and reported.

The Cochrane Collaborations's tool for assessing risk of bias (21) was used for the appraisal of the quality of the studies included.

Results

The results of the literature search and the progress through the different stages of the review process are depicted in the Quorom flow chart (**Figure 1**). A total of 36 publications met the inclusion criteria. The reasons for exclusion of the full text publications are given in **Table 1**. Two publications appeared to report different results of the same study (22;23). Therefore the total number of studies included in the review is 35. Twenty trials investigated the short to long term effect (3 d – 6 mo) of the dietary intervention and 15 studies investigated the effect from a previous meal on outcomes measured after the second meal (second meal studies). The detailed characteristics of the intervention trials are given in **Table 2** and that of the second meal studies in **Table 3**.

Figure 1 **Flow chart selection process**

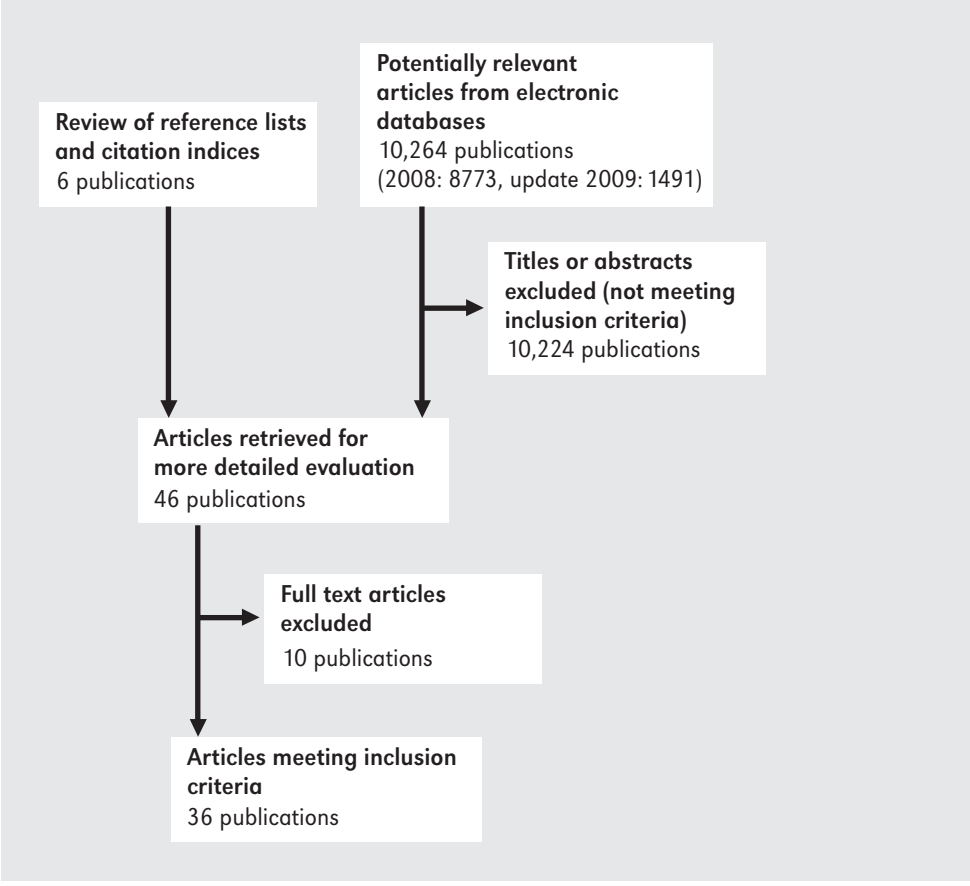

Table 1 **Reasons for exclusion of full text articles**

Article	Reason exclusion
Dumnesnil et al (24)	Differences in macronutrient composition
Fukagawa et al (25)	Differences in macronutrient composition
Frost et al (26)	No control intervention
Herrmann et al (27)	Difference in GI accomplished by altering mono- and disaccharide intake
Kallio et al (28)	Intervention differed in insulinemia not in glycemia
Kiens et al (29)	Difference in GI accomplished by altering mono- and disaccharide intake
King et al (30)	Fiber supplement was not derived from cereal grain
Park et al (31)	Differences in macronutrient composition
Pittas et al (32)	Differences in macronutrient composition
Wolever et al (33)	Glucose tolerance, insulin sensitivity not assessed

Risk of bias in included studies

In general the method of sequence generation and the blinding of outcome assessor were not reported. In most trials drop-out were reported but reasons for that were not always given. The wash-out periods were considered to be sufficient. In two trials, however, no wash-out period was reported. For details see **Table 4**.

Table 2 **Characteristics intervention trials**

Study	Design	Duration (wash-out)	Subjects	Age (y)[1] BMI (kg/m^2)[1]	Intervention	Outcomes
Andersson et al (34)	Randomized crossover	6 wk (6–8 wk)	30 healthy adults (22 female) with one or more of: elevated insulin, fasting glucose and triglycerides; reduced HDL cholesterol; borderline hypertension	59 ± 5 28 ± 2	Whole-grain vs refined-grain products	Body weight, insulin sensitivity, urinary 8-iso-prostaglandin F2α, interleukin 6, C-reactive protein
Aston et al (35)	Randomized crossover	12 wk (0 wk)	19 hyperinsulinemic women	52 ± 6 33 ± 5	High vs low-GI diet	Body weight and composition
Bouche et al (36)	Randomized crossover	5 w (5 wk)	11 healthy men	46 ± 3 28 ± 1	High vs low-GI diet	Body weight and composition, insulin sensitivity, leptin, non-esterified fatty acids
Brynes et al (37)	Randomized crossover	24 d (24 ± 2 d)	17 healthy men with one or more cardiac risk factors	45 ± 8 29 ± 4	High vs low-GI diet	Body weight, insulin sensitivity
Clapp et al (38)	Randomized crossover	20 d (1–3 mo)	7 healthy women, varied in age, race, fat mass, physical activity level	35 ± 8 27 ± 3	High vs low-GI diet	Body weight, insulin sensitivity, leptin, tumor necrosis factor α

Table 2 **Characteristics intervention trials** *(continued)*

Study	Design	Duration (wash-out)	Subjects	Age (y)[1] BMI (kg/m^2)[1]	Intervention	Outcomes
De Rougemont et al (39)	Randomized parallel	5 wk	38 healthy adults (19 female)	36 ± 2 and 40 ± 2[2] 28 ± 0.3 and 27 ± 0.3[2]	High vs low-GI diet	Body weight and composition, insulin sensitivity
Frost et al (40)	Randomized parallel	3 wk	28 women, healthy with (n = 16) and without parental history of CHD	30–39[3] 21–29[3]	High vs low GI diet	Body weight, insulin sensitivity, adipocyte size, non-esterified fatty acids
Garcia et al (22;23)	Randomized crossover	6 wk (6 wk)	11 adults (7 females) with insulin resistance and impaired glucose tolerance	56.5 ± 6.2 30.1 ± 5.7	High vs low cereal fiber diet (arabinoxylan concentrate)	Body weight and composition, glucose tolerance, adiponectin, resistin, leptin, non-esterified fatty acids
Hanai et al (41)	Crossover	6 mo (6 mo)	20 obese (10 females) and 8 non-obese (4 females) adults with impaired glucose tolerance 10 healthy adults (4 females)	35–68[3] obese: > 26.3 non-obese: 20–24	High vs low cereal fiber diet (corn bran hemicellulose)	Body weight, glucose tolerance
Juntunen et al (42)	Randomized crossover	8 wk (8 wk)	20 healthy postmenopausal women (3 impaired glucose tolerance)	59 ± 6 28 ± 3	High-fiber rye breads vs white wheat breads	Body weight, insulin sensitivity

Li et al (43)	Randomized crossover	4 wk (4 wk)	10 healthy women	20 ± 1 19 ± 2	Rice diet vs barley and rice diet	Glucose tolerance
Maki et al (44)	Randomized parallel	12 wk	60 adults (27 females) with elevated blood pressure	63 ± 2 57 ± 2 (control) 33 ± 1 32 ± 1 (control)	High vs low cereal fiber diet (oat beta-glucan)	Body weight, oxidized LDL, malonaldehyde, protein carbonyls
Ostman et al (45)	Randomized crossover	3 wk (3 wk)	7 women with impaired glucose tolerance	27–41[3] 28 ± 5	High GI breads vs low GI breads	Body weight, glucose tolerance, insulin sensitivity
Pal et al (46)	Randomized crossover	3 wk (3 wk)	21 overweight or obese adults with hypercholesterolemia (16 females)	25–65[3] 32 ± 0.6	High vs low GI breakfasts	Body weight and composition, insulin sensitivity
Pereira et al (47)	Randomized crossover	6 wk (6–9 wk)	11 hyperinsulinemic adults (6 females)	42 ± 3 30 ± 1	Whole-grain vs refined-grain products	Body weight, insulin sensitivity
Philippou et al (48)	Randomized parallel	4 mo	41 overweight adults	Not reported 32 ± 5	High vs low GI diet	Body weight and composition, insulin sensitivity, β-cell function
Robertson et al (6)	Randomized crossover	4 wk (4 wk)	10 healthy adults (6 females)	49 ± 3 23 ± 1	High resistant starch vs low resistant starch diet	Body weight and composition, insulin sensitivity, adiponectin

Table 2 **Characteristics intervention trials** *(continued)*

Study	Design	Duration (wash-out)	Subjects	Age (y)[1] BMI (kg/m^2)[1]	Intervention	Outcomes
Sloth et al (49)	Randomized parallel	10 wk	45 healthy overweight women	20–40[3] 28 ± 0.2	High vs low GI diet	Body weight and composition, insulin sensitivity
Weickert et al (50)	Randomized crossover	3 d (7 d)	17 overweight/obese women, normal fasting glucose, normal glucose tolerance	53 ± 9 30 ± 2	White bread vs oat fiber-enriched white bread	Body weight and composition, insulin sensitivity, adiponectin, non-esterified fatty acids
Wolever et al (51)	Randomized parallel	4 mo	34 adults (19 females) with impaired glucose tolerance	56 ± 2 31 ± 1	High vs low GI diet	Body weight, insulin sensitivity, glucose effectiveness, pancreatic responsivity, glucose disposition index

1 mean ± SD, unless otherwise stated;
2 mean ± SEM;
3 range

Table 3 **Characteristics second meal studies**

Study	Subjects	Age (y)[1] BMI (kg/m^2)[1]	First meal	Second meal (amount carbohydrates)	Time 2. meal (interval 1. and 2. meal)	Outcomes
Early second meal studies						
Brighenti F 2006 (52)	10 healthy adults (2 females)	40 ± 10 24 ± 3	High GI: Sponge cake with amylopectin (amioca) starch and cellulose Low GI: Sponge cake with slowly digestible starch (Hylon VII) and cellulose from hazelnut shells	Mixed meal (93 g)	Not given (after 5 h)	Difference in plasma glucose and insulin concentrations at single time points
Liljeberg 1999 (53)	10 healthy adults (6 females)	22–57 22 ± 2	White wheat bread, 4 high-amylose barley breads, white wheat bread with raw potato starch, spaghetti	Mixed meal (not given)	Not given (after 4 h)	Difference in plasma glucose and insulin concentrations at single time points
Liljeberg 2000 (54)	10 healthy adults (8 females)	24–51 21 ± 1	White wheat bread, spaghetti	Same as above	Not given (after 4 h)	Difference in plasma glucose and insulin concentrations at single time points

Table 3 **Characteristics second meal studies** *(continued)*

Study	Subjects	Age (y)[1] BMI (kg/m^2)[1]	First meal	Second meal (amount carbohydrates)	Time 2. meal (interval 1. and 2. meal)	Outcomes
Nilsson A 2008a (55)	12 healthy adults (5 females)	28 ± 5 22 ± 2	White wheat bread, wheat kernels, rye kernels, oat kernels, barley kernels, white wheat bread with barley fiber, barley porridge	Same as above	12.00 h (after 4 h)	Difference in plasma glucose concentrations at single time points
Wolever 1995 (56)	8 healthy adults (4 females)	25 ± 1 22 ± 1	High carbohydrate high GI and low GI meals, low carbohydrate high GI and low GI meals	Mixed meal (68 g)	Not given (after 4 h)	0–2 h AUC[2] and iAUC[3] of plasma glucose and insulin
Overnight second meal studies						
Granfeldt 2006 (57)	14 healthy adults (7 females)	24–34[4] 24 ± 3	Barley kernels, spaghetti, white bread	White bread (50 g)	Not given	0–95 min iAUC of plasma glucose and insulin
Nilsson 2006 (58)	15 healthy adults (6 females)	20–30[4] 22 ± 3	White bread, wheat kernels, pearled barley kernels, spaghetti, spaghetti with wheat bran	White bread (50 g)	8.00 h (after 10.30 h)	0–2 h iAUC of plasma glucose and insulin, free fatty acid concentrations

Nilsson 2007 (59)	20 healthy adults (10 females)	19–30[4] 22 ± 2	White bread, white bread with barley fiber, spaghetti with barley fiber, spaghetti with oat fiber, barley porridge	White bread (50 g)	8.00 h (after 10.30 h)	0–2 h iAUC of plasma glucose and insulin, free fatty acids concentrations
Nilsson 2008a (55)	12 healthy adults (5 females)	28 ± 5 22 ± 2	White wheat bread, barley kernels, white wheat bread with barley fiber	White bread (50 g)	8.00 h (after 9.30 h)	Difference in plasma glucose concentrations at single time points
Nilsson 2008b (60)	15 healthy adults (5 females)	26 ± 3 23 ± 2	White bread, ordinary barley kernels, high amylose barley kernels, high β–glucan barley kernels, white bread with resistant starch, white bread with resistant starch and dietary fiber		8.00 h (after 10.30 h)	0–2 h iAUC plasma glucose and insulin, interleukin 8, interleukin 6, adiponectin, free fatty acid concentrations
Robertson 2003 (61)	10 healthy adults (6 females)	23–65[4] 20–36[4]	24 h high vs low resistant starch diet: Basal diet supplemented with 4 ××x 25 g Novelose (60 g resistant starch) or 4 × 10 g waxy-maize starch	Chocolate drink (59 g)	Not given	Insulin sensitivity (HOMA, minimal model), non-esterified fatty acid concentrations
Stevenson 2005 (62)	7 healthy males (recreational athletes)	23 ± 3 ca. 21[5]	Mixed meal with whole wheat pasta or white bread	Mixed meal (139 g)	9.00 h (after 13 h)	0–3 h iAUC plasma glucose and insulin, free fatty acid concentrations

Table 3 **Characteristics second meal studies** *(continued)*

Study	Subjects	Age (y)[1] BMI (kg/m^2)[1]	First meal	Second meal (amount carbohydrates)	Time 2. meal (interval 1. and 2. meal)	Outcomes
Stevenson 2008 (63)	7 healthy females (recreational athletes)	24 ± 3 ca. 23[5]	Mixed meal with whole wheat pasta or white bread	Mixed meal (119 g)	9.00 h (after 13 h)	0–3 h iAUC plasma glucose and insulin, free fatty acid concentrations
Thorburn 1993 (64)	10 healthy adults (4 females)	21–30[4] 21–30[4]	Brown rice, pearl barley	Glucose drink (75 g)	Not given (after 14 h)	0–2 h iAUC plasma glucose and insulin, free fatty acid concentrations
Weickert 2005 (65)	14 healthy females	24 ± 2 21± 2	24-h high fiber vs low fiber diet: 3 times either white wheat bread, wheat fibre bread, oat fibre bread, resistant starch bread	White bread (50 g)	Not given (after 10 h)	0–3 h iAUC plasma glucose and insulin, non-esterified fatty acid concentrations

1 mean ± SD, unless otherwise stated;
2 area under the curve,
3 incremental area under the curve,
4 range,
5 calculated from mean body weight and height

Table 4 **Quality assessment of intervention trials**

Study	Sequence generation	Blinding outcome assessor	Blinding subjects[1]	Incomplete outcome data addressed	Wash-out period sufficient (cross-over)
Anderson et al (34)	Unclear	"Non-blinded"		4 drop-outs	Yes 6 wk
Aston et al (35)	Computer generated randomization chart	Not described		7 drop-outs, reasons given	No wash-out
Bouche et al (36)	Unclear	Not described		No drop-outs described	Yes 5 wk
Brynes et al (37)	Unclear	Not described		5 drop-outs, reasons given	Yes 24 d
Clapp et al (38)	Unclear	Not described		4 drop-outs, not different from rest	Yes 1–3 mo
De Rougemont et al (39)	Unclear	Not described		2 drop-outs in each group	N.A.2
Frost et al (40)	Unclear	Not described		No drop-outs described	N.A.
Garcia et al (22;23)	Unclear	"Single-blinded"	Yes	3 drop-outs, reasons given	Yes 6 wk
Hanai et al (41)	Not randomized	Not described	No	No drop-outs described	No wash-out
Juntunen et al (42)	Unclear	Not described		2 drop-outs	Yes 8 wk
Li et al (43)	Unclear	Not described		No drop-outs described	Yes 4 wk

Table 4 **Quality assessment of intervention trials** *(continued)*

Study	Sequence generation	Blinding outcome assessor	Blinding subjects[1]	Incomplete outcome data addressed	Wash-out period sufficient (cross-over)
Maki et al (44)	Unclear	"Double blind"	Yes	22 drop-outs in high fiber and 13 drop-outs in low fiber group	N.A.
Ostman et al (45)	Unclear	Not described		No drop-outs described	Yes 3 wk
Pal et al (46)	Unclear	"Single-blinded"		No drop-outs described	Yes 3 wk
Pereira et al (47)	Unclear	"Non-blinded"		1 drop-out; 2 incomplete data	Yes 6–9 wk
Philippou et al (48)	Unclear	Not described		No drop-outs described	N.A.
Robertson et al (6)	Unclear	Not described	Yes	No drop-outs described	Yes 4 wk
Sloth et al (49)	Unclear	Not described		2 drop-outs in HGI diet; 5 drop-outs in LGI diet	N.A.
Weickert et al (50)	Computer generated lists of random numbers	"Single-blinded"		1 incomplete data	Yes 7 days
Wolever et al (51)	Coin toss	Not described		2 drop-outs in high GI group	N.A.

1 as dietary treatment allowed,
2 not applicable

Data analysis
A meta-analysis was not undertaken because of the heterogeneity of the included studies with respect to quality, study design, interventions and methods of outcome assessment.

Studies investigating glucose tolerance and insulin sensitivity
In total 33 studies investigated the effect of the food characteristics of interest on glucose tolerance (GT) and insulin sensitivity (IS). Results will be summarized for intervention trials (n = 18) and the second meal studies (n = 15) separately.

Intervention trials
The characteristics of the dietary intervention and the results of the trials are listed in **Table 5**. From the 18 intervention trials 4 were conducted in subjects with hyperinsulinemia or impaired glucose tolerance (IGT), 13 in healthy overweight or lean subjects and one trial in subjects with IGT and in healthy (41). From the 5 trials in subjects with hyperinsulinemia or IGT 2 investigated the effect of addition of isolated CF to the diet (22;41), the other studies either CF-enriched breads (45), whole grain foods or low GI foods (51).

The 14 trials in healthy subjects examined the effect of diets with a low GI (36–40;46;48;49), whole grain foods (34) or addition of resistant starch (RS) (6), CF-enriched bread (42;50), barley (43) and isolated CF to the diet (41).

The diets administered in most of these trials differed in more than one of the characteristics of interest. Therefore, they were grouped according to the similarity of the dietary intervention and the detailed characteristics of the intervention foods or diets reported, that is: reduced or same postprandial glycemia in combination with increased or same cereal fiber intake. In the trials comparing low vs high GI diets no distinction was made between the types of dietary fiber. For that reason, results of the GI trials will be reported separately. The low GI diets contained either an increased amount of total dietary fiber (36;37;39) or the same amount (40;46;48;49) compared to the high GI diet. One study (38) did not report dietary fiber intake at all.

Table 5 **Characteristics of dietary interventions and results of intervention trials**

Study	Characteristics intervention vs control	Difference in amount dietary fiber, cereal fiber or resistant starch/day	Glycemic index or glucose response; intervention vs control	Improved glucose tolerance (GT), insulin sensitivity (IS) or β-cell function (BF) compared to control (method)	Decrease in bodyweight (BW), fat mass (FM), adipocyte size (AS); increase in lean body mass (LM) compared to control (method)	Effect on non-esterified fatty acids, adipokines, inflammation markers compared to control
Diet with and without added isolated cereal fiber or resistant starch						
Garcia et al (22;23)	Arabinoxylan concentrate from wheat vs placebo 2 × 5 g in bread roll and 5 g powder	Cereal fiber: 15 g total dietary fiber: ca 24 vs 39 g	Decreased[1]	GT: yes (MTT)[2]	BW: no FM: no (BOD POD®)	Fasting NEFA[3], adiponectin, leptin, resistin: no change; postprandial NEFA: no change
Hanai et al (41)	Corn bran hemicellulose (L-arabino-D-xylan) 2 × 5 g with meals	Cereal fiber: 12 g total dietary fiber: ca 15 vs 27 g	Decreased[1]	Persons with IGT[4] GT: yes (OGTT)[5] Healthy persons GT: no (OGTT)	BW: no	
Maki et al (44)	High fiber: Oat β-glucan enriched products and powdered form of oat β-glucan vs low fiber: ready to eat cold wheat based cereal, low-fiber hot cereal, maltodextrin powder	Cereal fiber: 11 g total dietary fiber 17 vs 28 g	Decreased		BW: no	Oxidized LDL, malonaldehyde, protein carbonyls: no change

Robertson et al (6)	30 g resistant starch/day (50 g Hi-Maize 260) vs 20 g rapidly digestible starch/day (20 g Amioca)	Resistant starch: 30 g total dietary fiber18 vs 48 g	Same	IS : yes (EHC)[6] IS: no (HOMA)[7] GT: yes (MTT) BC: no (HOMA-β)[8]	BW: no FM: no LM: yes	Fasting NEFA, leptin: no change; postprandial NEFA, leptin: no change; adipose tissue output NEFA: lower after high resistant starch
Breads enriched with cereal fiber vs bread with low content of cereal fiber						
Weickert et al (50)	Bread enriched with 10.4 g oat hull fiber (70 % cellulose, 25 % hemicellulose, 3–5 % lignin) vs white wheat bread; Breads provided at breakfast, lunch and 10:00 pm	31.2 g vs 0 g cereal fiber/day from the breads	same	IS: yes (EHC)	BW: no LM: no (Bioelectrical impedance analysis)	Fasting NEFA, adiponectin: no change
Juntunen et al (42)	High fiber rye bread (added rye bran) vs white wheat bread; 20 % of daily energy; breads provided; Rye bread diet significantly less fat and more protein	31 g total dietary fiber 14.4 vs 45.5 g	Same[9]	IS: no (FSIGTT)[10]	BW: no	
Ostman et al (45)	Rye kernels and oat bran concentrate; 7 slices/day	25–32 g cereal fiber and resistant starch vs 6 g per 100 g bread (dry weight)	Decreased	GT: yes (intravenous GTT) IS: no (Botnia clamp)	BW: no	

Table 5 **Characteristics of dietary interventions and results of intervention trials** *(continued)*

Study	Characteristics intervention vs control	Difference in amount dietary fiber, cereal fiber or resistant starch/day	Glycemic index or glucose response; intervention vs control	Improved glucose tolerance (GT), insulin sensitivity (IS) or β-cell function (BF) compared to control (method)	Decrease in bodyweight (BW), fat mass (FM), adipocyte size (AS); increase in lean body mass (LM) compared to control (method)	Effect on non-esterified fatty acids, adipokines, inflammation markers compared to control
Whole grain vs. refined grain diet						
Pereira et al (47)	Whole grain vs refined grain foods; Increased cereal fiber expected but only total dietary fiber measured All food provided; wheat based	12,8 g total dietary fiber 28 vs 17,8 g	Same	IS: yes (EHC) IS: yes (HOMA)	BW: no	
Andersson et al (34)	Whole grain vs. refined grain foods; increased cereal fiber expected but only total dietary fiber measured Cereal products provided; mainly wheat based	12,7 g total dietary fiber 17,3 vs 30 g	Same	IS: no (EHC)	BW: increased in whole grain group	Urinary 8-iso-prostaglandin F2α, fasting plasma IL 6, C-reactive protein: no change

Substitution of 30 % of 3 portions white rice/day with barley						
Liet al (43)	30 % of carbohydrates replaced with barley: 100 % rice or 30 % barley and 70 % rice; 3 whole meals/day provided; Increased cereal fiber expected but only total dietary fiber measured	13 g total dietary fiber 27 vs 40 g based on 70 kg person	Decreased[11]	GT: no (OGTT)		
Low vs high glycemic index						
Aston et al (35)	High GI vs low Gi diet High and low GI-food provided; ad libitum	3 g total dietary fiber 15 vs 18 g	56 vs 64		BW: no FM: no LM: no (DEXA)[12]	
Bouche et al (36)	High GI (GI > 60) vs low GI (GI < 45) Cereals and cookies provided; list of other carbohydrate items recommended; ad libitum	12 g total dietary fiber 19 vs 31 g	41 vs 71	IS: no (HOMA)	BW: no FM: yes (DEXA)	Fasting NEFA, leptin: no change
Brynes et al (37)	High GI vs low GI Written dietary advice; 700 g instant potato or 1200 g wholegrain rye bread provided respectively; ad libitum	12 g total dietary fiber 19 vs 31 g	48 vs 68	IS: no (HOMA) IS: yes (HOMA-PP)	BW: no	

Table 5 **Characteristics of dietary interventions and results of intervention trials** *(continued)*

Study	Characteristics intervention vs control	Difference in amount dietary fiber, cereal fiber or resistant starch/day	Glycemic index or glucose response; intervention vs control	Improved glucose tolerance (GT), insulin sensitivity (IS) or β-cell function (BF) compared to control (method)	Decrease in bodyweight (BW), fat mass (FM), adipocyte size (AS); increase in lean body mass (LM) compared to control (method)	Effect on non-esterified fatty acids, adipokines, inflammation markers compared to control
Clapp et al (38)	Low GI: whole grains, nontuberous vegetables, most fruits, nuts, dairy products vs high GI: processed flours, tuberous vegetables, ripe bananas, baked goods, candy and soft drinks All food prepared by research center kitchen; 10 days outpatient, last 10 days inpatient; ad libitum	Not given	59 vs 92	IS: yes (EHC) IS: yes (HOMA) IS: yes (QUICKI)[13]	BW: yes	Fasting leptin: lower after low GI diet Fasting tumor necrosis factor-α: no change
De Rougemont et al (39)	High GI foods GI > 70 vs low GI foods GI < 50; Individual guidance with lists of allowed/prohibited food products; high GI: extruded cereals provided; low GI: Precooked wheat in pouches, black bread, breakfast biscuits provided; ad libitum	7 g total dietary fiber 18 vs 26 g	< 50 vs >70	IS: no (QUICKI) IS: no (HOMA)	BW: yes FM: no (mono-frequency impedance)	

Frost et al (40)	High GI diet > 85: pasta, oats, whole grain products, pulse vegetables, whole fruit, no sucrose and lactose containing foods; low GI diet < 85: avoidance of foods taken in high GI diet; diets prescribed; ad libitum	Same total dietary fiber 19 vs 18 g	67–71 vs 87–89	IS: yes (short ITT)[14]	BW: no AS: no	NEFA during short ITT: no change
Pal et al (46)	High vs low GI breakfast; replacement meals provided	Same total dietary fiber 22 vs 20 g	Breakfast 35 vs 79 GI total diet not given	IS: no (HOMA)	BW: no FM: no (Bioelectrical impedance)	
Phillippou et al (48)	High GI vs low GI; dietary advice	Same total dietary fiber11 vs 13 g	50 vs 64	IS: no (HOMA) BC: no (HOMA-β)	BW: no FM: no (Bioelectrical impedance)	
Sloth et al (49)	High GI vs low GI; Carbohydrate-rich foods provided: products with finely milled vs intact whole grains respectively; ad libitum	Same total dietary fiber 31 vs 34 g	79 vs 102	IS: no (HOMA) BC: no (HOMA-β)	BW and FM: decreased in both groups LM: no (DEXA)	
Wolever et al (51)	High GI vs low GI lists of foods provided	13 g total dietary fiber 23 vs 36 g	54 vs 59	IS: no (FSIGTT) BC: no (pancreatic responsivitiy); yes (glucose disposition index)	BW: Decreased after control	

1 Lu Z et al; 2 meal tolerance test; 3 non-esterified fatty acids; 4 impaired glucose tolerance; 5 oral glucose tolerance test; 6 euglycemic hyperinsulinemic clamp; 7 homeostatic model assessment; 8 HOMA beta-cell function; 9 Juntunen K et al; 10 short intravenous GTT; 11 Foster-Powell et al; 12 Dual energy X-ray absorptometry; 13 quantitative insulin sensitivity check index; 14 insulin tolerance test

Intervention trials in subjects with hyperinsulinemia or impaired glucose tolerance

- Three trials examined the effect of foods with *increased CF* content that *reduced postprandial glycemia*. Two studies (23;41) reported increased GT (OGTT, MTT) as result of addition of a moderate amount isolated CF (12–15 g). A similar amount of CF supplied with CF-fiber enriched breads resulted also in improved GT (intravenous GTT) in the other study (45), but IS was not improved as assessed by an EHC following the GTT (Botnia clamp).
- One intervention trial with foods with *increased CF* content eliciting the *same postprandial glycemia* (whole grain foods) (47) reported improved IS (EHC, HOMA).
- One intervention trial with a *low GI* diet and increased amount of total dietary fiber (51) did not find an effect on IS (FSIGTT).

Intervention trials in healthy lean and overweight subjects

- Two intervention trials with foods with *increased CF* content that *reduced glycemia* (41;43) in lean volunteers had no effect on GT (OGTT).
- Four trials assessed the effect of foods with *increased CF or RS* content eliciting the *same postprandial glycemia*. Administration of either a high amount of RS (30 g) (61) or oat hull fiber (31 g) (50) resulted in improved IS (EHC). One study with a comparable amount of rye arabinoxylan (31 g) (42) showed no effect on IS (FSIGTT). A whole grain intervention with a moderate amount of CF (12 g) (34) also showed no effect on IS (EHC), but resulted in increased body weight.
- From 8 intervention trials that investigated the effect of foods with a *low GI* 2 reported improved IS (38;40). This was accompanied by decreased body weight in one trial (38). Another trial (37) observed no change in fasting IS (HOMA), but the IS after a meal (HOMA-PP) was significantly improved after the low GI intervention.

Second meal studies

Five second meal studies examined the effect of a breakfast on GT after lunch (early second meal studies) and 10 studies the effect of an evening meal on GT or IS after breakfast (overnight second meal studies). Improved GT was defined either as significantly lower blood glucose concentration at certain time points after the second meal or a lower incremental area under the blood glucose curve (g-iAUC) with or without lower insulin concentrations.

Early second meal studies

The characteristics of the breakfast meals tested with and without effect on GT are shown in **Table 6**. Only one of these studies used g-iAUC as measure of GT (56) (Table 3). Breakfasts with a low GI (≤ than 70) resulted in increased GT after lunch independent of the amount of RS and CF (2.2–27 g). Breakfasts with a GI ≥ 70 (11–18 g RS and CF) had no effect.

Overnight second meal studies

In 2 studies not only a single evening meals, but 3 (65) or 4 meals (61) on the day before the "second" meal differed in the characteristics of interest. GT was assessed in all but one study (Nilsson 2008a) by comparing the g- iAUC or applying a minimal model index approach (61) (Table 3).

The characteristics of the evening meals, that resulted in improved or unchanged GT or IS, can be found in **Table 7**. Improved GT after the standard breakfast was not related to the GI of the evening meal. The presence of a high amount of RS and CF (13.4–81 g) seemed to be more important. Products with intact barley kernels (55;57;58;64) were more effective than added isolated barley fiber (55;59) except in combination with RS (60). Addition of oat or wheat bran (13 g) to the meal (58;59) was not effective. However, RS (15 g) (61) as well as addition of wheat straw and oat hull fiber to bread (13.5 g) (65) had beneficial effects. White spaghetti (ca 80 g), spaghetti with added isolated wheat and oat bran or barley fiber (58;59) were not effective, whereas a large portion of wholemeal spaghetti (ca 140 g) improved GT (62;63).

Studies investigating body composition

Ten intervention trials measured the effect of the different dietary interventions on body composition. The food intake in those trials was ad libitum and the total energy intake was not different between the intervention and control diet. Seven trials in healthy volunteers (6;35;36;39;46;48;49) and one in volunteers with IGT (22) investigated the effect on fat mass (Table 5). Fat mass was decreased after intake of a high CF diet with decreased postprandial glycemia (36) without any change in total body weight. Four trials in healthy volunteers (6;35;49;50) examined the effect on lean body mass. One trial (6) found increased lean body mass after an intervention in lean volunteers with a high RS diet that did not change postprandial glycemia. Adipocyte size was measured by Frost et al (40) who did not find any differences.

Table 6 **Characteristics of meals of the early second meal studies**

Breakfast	Amount test meal (amount available carbohydrates) g	Glycemic index	Resistant starch (RS) g per meal	Dietary fiber (DF) g per meal	Total RS+ DF g per meal	Breakfast control	Amount test meal (amount available carbohydrates) g	Glycemic index	Resistant starch (RS) g per meal	Dietary fiber (DF) g per meal	Total RS+ DF g per meal
Breakfasts increasing glucose tolerance after lunch											
Sponge cake with slowly digestible starch (Hylon VII) and cellulose from hazelnut shells (52)	Not given (75)	Lower glucose response than after control	13	5	18	Sponge cake with amylopectin (amioca) starch and cellulose	Not given (75)	Not given	1	5	6
High-amylose barley bread with added β-glucan rich barley flakes baked for 20 h at low temperature (53)	115 (50)	60	11.2	25	27	White wheat bread	123 (50)	100	0.1	2	2.1
Spaghetti (white durum wheat flour) (53)	74[1] (50)	52	0.2	2	2.2	Same as above					
Spaghetti (white durum wheat flour) (54)	Same as above					Same as above					
Barley kernels (55)	96[1] (50)	49 ± 7	8.0	9.1	17.1	White wheat bread	119 (50)	100	0.8	4.3	5.1
Psyllium-enriched oat cereal with milk and orange juice (56)2	Not given (84)	70	Not given	Not given		Cornflakes with milk and orange juices	Not given (84)	102	Not given	Not given	

Breakfasts not increasing glucose tolerance after lunch											
High-amylose barley bread (53)	159 (50)	99	1.4	10	11.4	White wheat bread	123 (50)	100	0.1	2	2.1
High-amylose barley bread with preboiled barley baked for 20 h at low temperature (53)	212 (50)	83 ± 10	6.8	12	18.8	Same as above					
High-amylose barley bread baked for 20 h at low temperature (53)	164 (50)	71	5.1	11	16.1	Same as above					
White wheat bread with raw potato starch (53)	122 (50)	92 ± 16	9.7	2	11.7	Same as above					
Barley porridge (55)	116 (50)	112 ± 25	2	9	11	White wheat bread	119 (50)	100	0.8	4.3	5.1
White wheat bread with barley fiber (55)	95 (50)	93 ± 15	1	13	14	Same as above					
Oat kernels (55)	119[1] (50)	85 ± 13	4	8	12	Same as above					
Wheat kernels (55)	91[1] (50)	73 ± 13	5	8	13	Same as above					
Rye kernels (55)	93[1] (50)	73 ± 19	4	14	18	Same as above					

1 dry weight;
2 statistically different only when incremental and not total area under the curve is considered

Table 7 **Characteristics of meals of the overnight second meal studies**

Evening meal	Amount test meal (amount available carbohydrates) g	Glycemic index	Resistant starch (RS) g per meal	Dietary fiber (DF) g per meal	Total RS and DF g per meal	Evening meal control	Amount test meal (amount available carbohydrates) g	Glycemic index	Resistant starch (RS) g per meal	Dietary fiber (DF) g per meal	Total RS and DF g per meal
Meals resulting in increased glucose tolerance/insulin sensitivity after the standard breakfast											
Pearl barley (64)	345 (90)	Not given	4.5	11.7	16.2	Brown rice	357 (90)	Not given	2.4	2.2	4.6
High amylose maize starch Novelose (61)	4 × 25 (10)	Not given	4 × 15	0	15	Waxy maize starch	4 × 10 (10)	Not given	0	0	0
Wheat bread with fiber made from wheat straw: (95 % insoluble)(65)	3 × 131 (50)	Postprandial glucose response as white wheat bread	Not given	3 × 13.4	13.4	White wheat bread	3 × 103 (50)			3 × 2.9	2.9
Wheat bread with fiber made from oat hull (93 % insoluble) (65)	3 × 133 (50)	Postprandial glucose response as white wheat bread	Not given	3 × 13.5	13.5	Same as above					
Whole wheat pasta and meat (62;63)	132 (90)[1] for 60 kg person	33.7	Not given	8.9		White bread and meat	136 (127)	71.6	Not given	4	
Barley kernels (57)	79.6 (50)	53	7.6	8.5	16.1	White wheat bread	120.5 (50)	100	0.1	2.0	2.1

Barley kernels (58)	83.7 (50)	54	7.3	9.8	17.2	White wheat bread	119.9 (50)	100	0.5	3.0	3.5
Barley kernels (55)	96 (50)	49 ± 7	8.0	9.1	17.1	White wheat bread	119 (50)	100	0.8	4.3	5.1
Bread with whole barley kernels (60)	161 (50)	52	9.5	10.7	20.2	White wheat bread	117 (50)	100	1.3	2.6	3.9
Bread with cut barley kernels (60)	190 (50)	55	8.8	10.6	19.4	Same as above					
High amylose barley bread (60)	213 (50)	52	22.0	16.1	38.1	Same as above					
High β-glucan barley bread (60)	388 (50)	50	30.9	50.1	81.0	Same as above					
White wheat bread with resistant starch and barley fiber (60)	182 (50)	88	8.8	10.3	19.1	Same as above					
Meals not affecting glucose tolerance/insulin sensitivity after the standard breakfast											
Bread with resistant starch Hi-maize 1043 (65)	3 × 123 (50)	Postprandial glucose response as white wheat bread	3 × 6.2	3 × 2.9	9.1	White wheat bread	3 × 103 (50)			3 × 2.9	2.9
Spaghetti (57)	72.3 g (50)	58	0.2	2.0	2.2	White wheat bread	120.5 (50)	100	0.1	2.0	2.1

Table 7 **Characteristics of meals of the overnight second meal studies** *(continued)*

Evening meal	Amount test meal (amount available carbohydrates) g	Glycemic index	Resistant starch (RS) g per meal	Dietary fiber (DF) g per meal	Total RS and DF g per meal	Evening meal control	Amount test meal (amount available carbohydrates) g	Glycemic index	Resistant starch (RS) g per meal	Dietary fiber (DF) g per meal	Total RS and DF g per meal
Wheat kernels (58)	86 (50)	54	10.4	10.1	20.5	White wheat bread	119.9 (50)	100	0.5	3.0	3.5
Spaghetti (58)	76.6 (50)	52	2.6	3.1	5.7	Same as above					
Spaghetti with 11.6 wheat bran (58)	88.3 (50)	52	2.6	12.5	15.1	Same as above					
Spaghetti with 18.8 g barley fiber (59)	70.9 (50)	Not given	2.8	12.9	15.7	White wheat bread	126 (50)	100	0.5	2.6	3.1
Spaghetti with 23.9 g oat bran (59)	69.7 (50)	Not given	2.8	12.7	15.5	Same as above					
Barley porridge (59)	79.4 (50)	97	0.7	8.5	9.2	Same as above					
White wheat bread and barley fiber (55)	95 (50)	93 ± 15	0.8	12.9	13.7	White wheat bread	119 (50)	100	0.8	4.3	5.1
White wheat bread with resistant starch (Hi-maize) (60)	130 (50)	76	8.0	3.5	11.5	White wheat bread	117 (50)	100	1.3	2.6	3.9

1 estimated from menu given (NEVO table)

Studies investigating non-esterified fatty acid concentrations
In 5 intervention trials in healthy volunteers (6;36;40;50) or volunteers with IGT (23) plasma non-esterified fatty acid (NEFA) concentrations were measured. Neither fasting nor postprandial NEFA concentrations were changed (Table 5). The results of 8 second meal studies were not consistent. In *early* second meal studies NEFA concentrations before intake of the standard lunch were lower after the low GI breakfast in one study (56) but suppression after lunch was the same (52;56). In *late* second meal studies fasting NEFA concentrations in the morning after an evening meal rich in non-digestible carbohydrates were lower in 3 studies (58;64;66) and the same in 3 other studies (59;61;65). NEFA suppression after the breakfast was the same in three studies (59;64), whereas a greater suppression of NEFA was observed in the late postprandial period after breakfast by Robertson et al (61) and Weickert et al (65).

Studies investigating adipokine response
Five intervention trials in healthy volunteers (6;36;38;50) or volunteers with IGT (22) measured the adipokine concentrations in plasma, of which one trial reported lower fasting leptin concentrations after a low GI intervention (38) (Table 5). In one overnight second meal study (60) a significant increase in fasting adiponectin in the morning after the intake of an evening meal rich in CF and RS starch was observed. After the intake of a standard breakfast this difference disappeared.

Studies investigating markers of oxidative stress and inflammation
No effect of dietary interventions with increased CF (34;44) or low GI (38) was found on markers of oxidative stress and inflammation (Table 5). One overnight second meal study (60) observed a lower IL 6 concentration in the morning after the intake of an evening meal rich in dietary fiber and RS, but no change in IL 8.

Studies investigating β-cell function
Beta-cell responsiveness, calculated as the area under the insulin response curve for 10 min after intravenous glucose infusion (FSIGTT) was not significantly different between high and low GI diet in IGT subjects, but an improved disposition index (more insulin secreted for a given change in plasma glucose concentration) was reported (51). β-cell function estimated by (HOMA-β) did not change after an intervention with RS (6) nor after two interventions with low versus high GI food (48;49). (Table 5)

Discussion

In observational studies, the reduction of postprandial glycemia and a high content of non-digestible carbohydrates (and CF-associated micronutrients or phytochemicals) are characteristics of starchy foods that are implicated with the prevention of T2DM. This review identified 35 experimental human studies, which were used to derive the relative importance of those characteristics on factors associated with the development of T2DM.

The most striking result of this review is the lack of evidence for a effect of interventions with low GI on IS, as only 2 (37;40) of 9 trials observed a beneficial effect independent of a change in body weight. This lack of effect is surprising as many prospective studies report preventive effects of low GI diets on the development of T2DM. Reasons for this could be, that most trials reporting negative results, assessed IS with fasting measures (HOMA, QUICKI) which represent hepatic IS (67). Positive results were observed either after an insulin or glucose challenge (short ITT or HOMA-PP) reflecting whole body IS. As postprandial hepatic glucose disposal accounts only for 30 % of the total postprandial glucose disposal, this could suggest that reduced glycemia selectively improves peripheral IS. Accordingly, it has been hypothesized that "diet predominantly affects mechanisms associated with peripheral insulin action" (10), because a diet-related effect on peripheral but not on hepatic IS has been observed in a 5-y trial in persons with impaired glucose tolerance (68). Therefore, the choice of outcome measure seems to require more thorough consideration. In addition, information of the effect of low GI diets on GT or IS in persons with IGT are lacking, because all but one trials were conducted in volunteers with normoglycemia. The results of our review are not in agreement with that of another systematic review on this topic (69), which reported improved IS in healthy subjects after low versus high GI diets. In this review the results of the intervention trials were pooled and a meta-analysis performed, which makes direct comparison difficult. More importantly, different trials were the base of this meta-analysis due to different selection criteria and the time point of the search, which was January 2005.

The results of 6 interventions in healthy volunteers with an increased amount of non-digestible carbohydrates on GT and IS were not conclusive. Two trials observed improved IS after increased consumption of RS or CF-enriched breads, whereas interventions with whole grain foods, breads enriched with rye bran or isolated corn-bran hemicellulose did not show any effect. Here, the effect does not

seem to be related to the method of assessment as none of the studies assessed isolated hepatic IS. Discrepancies in results could be due to different amounts or types of non-digestible carbohydrates used. The positive effect in both trials can solely be ascribed to the increase in non-digestible carbohydrates because the interventions did not affect postprandial glycemia.

The most consistent results were derived from the 4 intervention trials with persons with IGT or hyperinsulinemia, which all showed that GT or IS improved after diets with moderately increased amounts of CF. Methods of assessment were the OGTT/MTT as well as EHC. The increase in CF content of the diet was achieved either with isolated CF (arabinoxylan) or whole grain products or a combination of both (addition of oat bran concentrates and rye kernels to bread). In 3 of these trials, glycemia was lower after the CF-supplemented meals which were taken 2–3 times per day. However, the interventions in healthy volunteers with whole grain products and the RS and CF-enriched bread supplementation also improved GT or IS, despite the fact that the postprandial glycemia was not different from that of the control intervention. Therefore, it has to be considered that properties other than the blood glucose lowering effect of non-digestible carbohydrates could be responsible for the effect observed.

A large number of studies investigated the effect of the characteristics of a first meal on the GT after a second meal in healthy persons. The results of these studies have not been summarized before. Improved GT to the second meal in *early* second meal studies was observed after breakfasts with low GI which had a low content of RS or CF. However, in most *early* second meal studies only differences in single time points of plasma glucose following the second meal were reported. This makes the effects less convincing than those derived from most *overnight* second meal studies, in which the area under the glucose curve after the subsequent meal was shown to be different. In the *overnight* second meal studies the type of CF and combination with RS was more important than postprandial glycemia of those foods for exerting the beneficial effect, suggesting a different underlying mechanism to that of the early second meal effect. The results of these studies highlight the potency of certain (combinations of) non-digestible carbohydrates to acutely influence GT, even in healthy volunteers. The reason why some combinations of CF and RS did not exert an effect is not clear and needs to be examined in more detail. Whether the same underlying mechanism is responsible for the beneficial effect observed in intervention trials also merits further investigation.

In summary, currently, there seems to be more evidence for the beneficial effect of non-digestible carbohydrates on GT and IS than for the reduction of postprandial glycemia. But what could be the plausible underlying biochemical mechanisms to explain these observations?

Firstly, the CF used in the interventions are (partly) fermented by the colonic microbiota resulting in an increased production of fermentation products, like the short chain fatty acids (SCFA) acetate, propionate and butyrate. These SCFA are rapidly absorbed from the colonic lumen and especially butyrate is an important energy source for colonic epithelial cells. However, a proportion of them also enter the portal and peripheral circulation and have been shown to exert effects on liver and adipose tissue (6–8). None of the intervention trials and few second meal studies (58;59;61;65) measured fermentation products in blood and results are not consistent. This could be due to low concentrations in the peripheral circulation, which are in the micromolar range and require sensitive analytical techniques. However, increased excretion of hydrogen in breath, an indicator of colonic fermentation, was observed in all but one studies the morning after the meals that increased GT. As a rise in colonic fermentation suggests a rise in the concentration of SCFA, assuming increased portal and peripheral SCFA concentrations seems reasonable. However, the way in which SCFA exert their beneficial effect on GT or IS requires further investigation. Proposed effects of SCFA on glucose metabolism are insulin-like properties of propionate (6), decrease of NEFA concentrations through indirect anti-lipolytic effects on adipose tissue (70) or anti-inflammatory effects (71). Only one study so far examined the direct effect of SCFA (72): oral supplementation of butyrate (5 g/kg/day) prevented the development of insulin resistance and obesity in C57BL/6J mice on a high-fat diet. Cell culture experiments to explore the underlying molecular mechanisms of their observation showed the potency of butyrate to directly activate among others adenosine 5'-monophosphate activated protein kinase (AMPK).The activation of AMPK by pharmacological means previously has been shown to increase glucose transport and cell-surface GLUT 4 content in skeletal muscle from nondiabetic men (73). Thus, there are indications for beneficial effects of SCFA which need to be studied more extensively. Secondly, an increased intake of CF is accompanied with an increased intake of micronutrients and phytochemicals as these components are present in the outer layer of the kernel and bound in cell wall components like arabinoxylan. These components can be released during fermentation in the

large intestine and might induce an anti-inflammatory effect (74;75), which will be discussed below.

To be able to distinguish between both these possible mechanisms, results of trials using RS which is devoid of phytochemicals are necessary. So far, only the intervention trial and overnight second meal study of Robertson et al (6;61) investigated the effect of RS supplementation and reported improved IS. This indicates an important role for colonic SCFA, which needs further confirmation.

The potency of decreasing low-grade inflammation as a strategy to prevent T2DM has recently been established with the anti-inflammatory drug salsalate (76;77), which emphasizes the relevance of also exploring the anti-inflammatory effect of food and food components. Whole grain foods contain a high number of micronutrients and phytochemicals as compared to refined grain foods, which are released during the small intestinal digestion as well as colonic fermentation and have the potency to reduce oxidative stress and inflammation (74). Results of a limited number of animal studies using polyphenol rich cereal fractions or a whole grain diet offer some support for this hypothesis (74;78;79). However, until now only two human intervention trials measured biomarkers of oxidative stress and inflammation after interventions differing in the amount of CF. They failed to confirm this observation.

Hyperglycemia has been shown to affect pathways of oxidative stress and inflammation. This phenomenon is not only seen as a result of diabetic hyperglycemia but also as a result of the acute postprandial response in healthy volunteers to high GI food (80). Recent studies have shown that ingestion of a 50–75 g glucose load or 50 g of rapidly digestible starch (white bread) results in the formation of reactive oxygen species (81;82) and the activation of NF-κB-binding activity in mononuclear cells in the postprandial phase. In vitro, high glucose concentrations induce toll-like receptor 2 and 4 expression in human monocytes which leads to increased NF-κB activity and IL 6 and TNF-α secretion (83). The relevance of this activation and increased inflammation in the postprandial period – if exerted chronically – is not clear and needs to be investigated in long term trials. So far, only one intervention trial aimed to examine the effect of a dietary intervention with food that reduced postprandial glycemia on circulating TNF-α and did not find any effect.

This review provides a comprehensive overview of effects that can be ascribed to specific characteristics of starchy foods on several factors implicated in the pathogenesis of T2DM. It was demonstrated that interpretation of results of intervention trials can be hampered when more than one food characteristic is

altered. If this is not recognized the effects of foods or diets can be misinterpreted which also hinders exploration of the underlying mechanism of the observed beneficial effects. Besides assessing outcomes of GT and IS, other intermediate endpoints, like body composition, inflammation markers and adipokine response, that receive increasing attention, were included. However, the results of these studies are inconclusive. Some of the outcomes assessed require further validation of their predictive value for the development of T2DM. Another limitation of our review is that some of the studies included were of limited methodological quality. In addition, some intervention trials were of short duration and also studies were included that investigated a relatively short term effect (second meal). However, as the main aim of the review was to derive information about the relative importance of the specific food characteristics and underlying mechanisms, it was felt that the results of these studies could contribute valuable information.

In conclusion, there is no evidence for a beneficial effect of decreased postprandial glycemia on hepatic IS and only limited evidence for a beneficial effect on GT or whole body IS in overweight, glucose tolerant persons. To be able to draw a definite conclusion about the possible beneficial effects of diets with low GI, more trials with measures of whole body IS are needed, which preferably also include persons with IGT or hyperinsulinemia. The intake of total dietary fiber and cereal fiber has to be controlled; otherwise distinction between the effects of decreased glycemia and an increased amount of non-digestible carbohydrates is not possible.

More evidence is currently available for a beneficial effect of increased consumption of non-digestible carbohydrate on GT and IS, independent of any effect on postprandial glycemia. The underlying mechanism needs to be further explored in studies in which the effect of colonic SCFA and the presence of bioactive compounds can be distinguished. In case SCFA production is the key factor, methods to monitor concentrations of SCFA either in plasma or urine need to be developed. No conclusion can be drawn concerning the effect of increased intake of micronutrients and phytochemicals present in cereal grains on oxidative stress or inflammation markers, as only a few trials were conducted with a great variety of markers.

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